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(57) Abstract

Compositions containing at least one compound with Growth Factor-like activity are used for the prophylactic treatment of a gastrointestinal condition at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug (e.g. indomethacine).

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PREVENTION OF GASTROINTESTINAL DAMAGE.

The present invention relates to the prevention of gastrointestinal damage and more particularly, but not exclusively, to such damage which occurs in the intestine.

There are a variety of gastrointestinal conditions in which damage to epithelial type cells occur. For example, this damage may be in the form of ulceration, increased permeability with protein and blood loss from the intestine or structuring.

Gastrointestinal conditions involving damage to epithelial cells arise after prolonged administration of Non Steroidal Anti-inflammatory Drugs (NSAIDs) (e.g. indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac, asprin etc) to patients who require protection from chronic inflammatory medical conditions. Examples of such chronic conditions which require prolonged administration of NSAIDs are rheumatoid arthritis and osteoarthritis. NSAID therapy is also beneficial for sufferers of Cystic Fibrosis (to ameliorate the inflammatory process causing lung damage). Long term use of NSAIDs is associated with a high risk of developing gastric or intestinal damage including structuring, fibrosis and ulceration. A major effect of NSAIDs is damage to gastrointestinal epithelial cells which may lead to the development of ulcers. Such ulcers may unexpectedly haemorrhage or become perforated. This leads to the requirement for emergency treatment and when undetected may even be associated with mortality. Mortality is especially associated with patients on NSAIDs who develop ulcers that become perforated because these patients are often symptomless and do not suffer pain because of the pain dampening effects of NSAIDs.

Up to 60% of NSAID-taking patients complain of dyspepsia or generalised abdominal discomfort. It has also been reported that gastric ulceration occurs in 12-30%, and duodenal lesions in 2-19%, of long term NSAID users. When it is considered that NSAIDs account for 5% of prescribed drugs in the UK but account for 25% of all reported adverse effects, it is apparent that these adverse effects associated with NSAIDs are a major problem and that a satisfactory means of preventing

NSAID-induced damage to gastrointestinal epithelial cells would be of considerable benefit.

Various measures are used to treat NSAID-induced ulcers. These include the use of several types of pharmaceutical products, such as Histamine H_2 receptor antagonists, sucralfate, prostaglandins (e.g. misoprostol) and hydrogen-potassium pump inhibiting agents (e.g. omeprazole). A major disadvantage of these products is that, although they are effective at treating gastric damage, they are largely ineffective when directed towards intestinal epithelium. It is therefore desirable that there is an agent which is effective for intestinal epithelium. It is particularly desirable that there is a suitable agent that may be used prophylactically to prevent gastrointestinal damage occurring. For instance, it would be of great beneficial to treat someone prophylactically if it is anticipated they will require NSAID therapy in order that gastrointestinal damage may be avoided. For example, prophylactic treatment would be of benefit for sufferers of rheumatoid arthritis, osteoarthritis or cystic fibrosis who are taking NSAIDs.

It is an object of the present invention to obviate or mitigate the above mentioned disadvantages and provide a prophylactic agent that may be used to prevent damage occurring to gastrointestinal epithelium as a result of administration of NSAIDs.

According to a first aspect of the present invention, there is provided the use of a composition containing at least one compound with Growth Factor-like activity for the manufacture of a medicament for prophylactic treatment of a gastrointestinal condition at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug.

According to a second aspect of the present invention, there is provided a method for the prophylactic treatment of a gastrointestinal condition that is at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug, the method comprising administering to a person or animal in need of such treatment a therapeutically effective amount of a composition containing a compound with Growth Factor-like activity.

By "prophylactic treatment" we mean either (i) a treatment that protects gastrointestinal epithelium such that a gastrointestinal condition that is at least partially characterised by damage to epithelial cells does not occur; or (ii) a treatment that prevents healthy epithelial cells from becoming damaged if a gastrointestinal condition already exists.

The invention is applicable for prophylactic treatment of patients who are at risk of suffering NSAID-induced damage to gastrointestinal epithelial cells (such as sufferers of rheumatoid arthritis, osteoarthritis or cystic fibrosis who are taking NSAIDs). Therefore the composition containing at least one compound with Growth Factor-like activity may be used to prophylactically prevent damage caused by NSAIDs such as indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac or asprin.

We have found that compositions containing at least one compound with Growth Factor-like activity are effective at prophylactically treating gastrointestinal conditions that are at least partially characterised by damage to epithelial cells as a result of NSAID administration. Examples of such compounds include naturally produced Growth Factors that have been isolated from the organism in which they were synthesised, Growth Factors produced by cell culture or fermentation of Growth Factor expressing cells, artificially synthesised Growth Factors, modified Growth Factors produced from genetically engineered organisms, compounds which activate Growth Factor receptors (Growth Factor receptor agonists), compounds which regulate growth factor intracellular signalling and compounds which influence Growth Factor synthesis or breakdown.

It is preferred that the composition containing at least one compound with Growth Factor-like activity is a composition containing at least one compound with activity similar to that of Growth Factors obtainable from colostrum. We have found that the specific type and quantity of Growth Factors obtainable from colostrum are particularly effective at preventing damage to gastrointestinal epithelial cells. A most preferred composition for use according to the invention is colostrum or a derivative thereof which contains viable Growth Factors.

Colostrum is the milk secreted by the mammary gland during the first 48 hours following parturition. The composition of this "first milk" is fundamentally different to that of the subsequently secreted normal milk. In particular, colostrum contains specific types and increased concentrations of growth factors. The colostrum used in the present invention is preferably the milk obtained in the first 2 milkings following parturition. Derivatives of such milk may also be used.

The particular effectiveness of colostrum or a derivative thereof is surprising because we have found that administration of Growth Factors provided by normal milk, or a derivative thereof, to a subject in need of prophylactic treatment is much less effective for preventing such damage than administration of Growth Factors obtainable from colostrum or a derivative thereof.

Compositions for use in the invention may contain an IGF (e.g. IGF-1 or IGF-2), a transforming growth factor (e.g. TGFβ1, TGFβ2 or TGFβ3), a keratinocyte growth factor, a fibroblast growth factor, and/or a platelet-derived growth factor.

Our studies have also established that members of the Transforming Growth Factor β (TGFβ) family of growth factors are particularly effective for protecting gastrointestinal epithelium. It is therefore preferred that compositions used in accordance with the invention contain a TGFβ, e.g. TGFβ1, TGFβ2 and/or TGFβ3. Compositions containing said TGFβ may be derived from any source, although it is preferred that such compositions are derived from colostrum.

While we do not want to be bound by any hypothesis, it is possible that these compositions protect epithelial cells by regulating apoptosis or regulating modelling of the extracellular matrix in the gastrointestinal tract.

It is preferred that compositions used in accordance with the invention are administered at least once daily. Prophylactic treatment with compositions containing at least one compound with Growth Factor-like activity may continue until the risk of gastrointestinal damage occurring has been removed. It is also preferred that the composition is administered from 6 to 72 hours (more preferably from 24 to 48) in advance of initiation of NSAID therapy and should ideally continue until NSAID therapy has stopped.

It will be appreciated that the amount of a composition containing at least one compound with Growth Factor-like activity required for prophylactic treatment of a (NSAID induced) gastrointestinal condition that is at least partially characterised by damage to epithelial cells depends on a number of factors. These include:

A) The efficacy of compounds with Growth Factor-like activity within the composition.

B) The amount of compounds with Growth Factor-like activity within the composition.

C) The severity of the condition to be treated.

D) The age of the subject to be treated.

We have established that the abovedescribed compositions are effective for preventing gastrointestinal epithelial damage if a person or animal in need of treatment receives from 0.1 to 5000μgrammes/day of compounds with Growth Factor-like activity. It is preferred that subjects receive from 50 to 2000μgrammes/day of compounds with Growth Factor-like activity and most preferred that subjects receive from 100 to 1000μgrammes/day of compounds with Growth Factor-like activity.

If a TGFβ is to be used for prophylactic treatment, then from 0.05 to 2500 μgrammes/day is a suitable amount to have a protective effect on gastrointestinal epithelium. It is preferred that from 25 to 1000μgrammes/day of said TGFβ is administered to a subject in need of treatment and most preferred that from 50 to 500μgrammes/day said TGFβ is administered.

Compositions containing at least one compound with Growth Factor-like activity may be administered in various ways. Thus a medicament of the invention may take a number of different forms. For example, the medicament may be in the form of a powder, tablet, capsule, liquid, food product or drink product or any other suitable form that may be administered to a person or animal. Food products (such as confectionery bars) and drink products are particularly preferred. These products may also contain flavouring, carbohydrates, a nitrogen source, vegetable oils, emulsifiers, oils containing long chain fatty acids, antioxidants, vitamins, soluble fibre, minerals,

other trace elements and the like to meet nutritional requirements and to make such products more palatable.

It will be appreciated that the vehicle for the composition should be one which is well tolerated by the subject to whom it is given and enables delivery of the active composition to the gastrointestinal tract.

The composition used according to the invention is preferably administered by an enteral route. However, Growth Factor-like activity in certain compositions (containing growth factors) is lost when administered by an enteral route. We believe this is due to digestion by luminal proteases. For this reason it is particularly preferred that a composition for enteral administration is colostrum or a derivative thereof. We have found that administration of compounds with Growth Factor-like activity within colostrum, or a derivative thereof, surprisingly protects the compound contained therein from being degraded and thereby allows the delivery of active compounds to gastrointestinal epithelium.

The route of enteral administration may be by means of an enema, a nasogastric tube or alternatively by means of gastrostomy tubes or jejunostomy tubes. A most preferred route of enteral administration is by an oral route.

Use of colostrum, or a derivative thereof, for prophylactic treatment of gastrointestinal conditions offers many advantages over therapies currently being used. For instance, large quantities of bovine colostrum can be readily obtained from dairy cattle. This means there are sufficient resources for the wide scale prophylactic use of compositions containing at least one compound with Growth Factor-like activity that are derived from colostrum. Furthermore, bovine colostrum is a natural and safe resource.

We have established that, to provide sufficient Growth Factors to have a protective effect on gastrointestinal epithelium, bovine colostral whey is preferably administered in the range of from 30 to 300mls/day. From 0.1 to 60.0 grammes/day represents a suitable daily dosage of spraydried derivatives of bovine colostrum. It will be appreciated that the amount of a colostrum derivative required will depend

upon the precise extraction or purification steps undertaken to prepare such a colostrum derivative.

The colostrum used in the invention as a source of compounds with Growth Factor-like activity is preferably bovine colostrum. Preferred colostrum derivatives are therefore derivatives of bovine colostrum.

As indicated earlier a colostrum derivative may be used in accordance with the invention. Such colostrum derivatives are those which contain the viable compounds with Growth Factor-like activity that may be found in colostrum. Examples of preferred colostrum derivatives are:

1. Colostrum may be spraydried to form a powder before being used. If desired the spraydried derivative may be reconstituted in the form of a spraydried skimmed milk drink. The colostrum may be defatted before spray drying if desired.

2. Colostral whey or a derivative thereof. Colostral whey is colostrum from which casein proteins have been removed. Derivatives suitable for use according to the invention include ultrafiltered or microfiltered fractions of colostral whey. These fractions contain more concentrated Growth Factors relative to remaining colostral proteins and nutrients. Colostral whey may be used in liquid form (which may be defatted if desired) or may be further treated (such as being spraydried) before use according to the invention.

As stated above, a most preferred composition of the invention is bovine colostrum or a derivative thereof. The colostrum may be obtained by normal milking procedures, after which it may be pooled and frozen prior to being processed, if desired, to produce a colostrum derivative.

If desired, the colostrum (or derivative thereof) may be supplemented with one or more growth factors (e.g. purified growth factors) such as an IGF (e.g. IGF-1 or IGF-2), a transforming growth factor (e.g. TGFβ1, TGFβ2 or TGFβ3), a keratinocyte growth factor, a fibroblast growth factor, and/or a platelet-derived growth factor.

Colostrum, or a derivative thereof, may be formulated with other agents to form a composition suitable for enteral consumption. For instance, agents such as carbohydrates, a nitrogen source, vegetable oils, emulsifiers, oils containing long

chain fatty acids, antioxidants, vitamins, soluble fibre or minerals and other trace elements may be included in the composition to fulfil nutritional requirements when colostrum is being incorporated into a food product (such as a confectionery bar) or drink product (in which case a liquid derivative or a powder derivative reconstituted as a liquid may be used). Alternatively derivatives of colostrum may be formulated with suitable excipients, stabilizers and the like to make a tablet, capsule or liquid medicament.

Additionally flavouring may also be included to make the composition more palatable.

The invention is illustrated by the following non-limiting example with reference to the accompanying drawings, in which:

Figure 1 represents the results of Example 1 for determining the effect of a colostrum derivative on indomethacin induced damage of gastrointestinal epithelium in mice; and

Figure 2 represents the results of Example 2 for determining the effect of TGFβ on indomethacin induced damage of gastrointestinal epithelium in rats.

EXAMPLE 1

METHODS

1. *In vivo* model of small intestinal injury

Protocol:

Mice were randomised into groups of twenty and fed on a standard chow diet *ad libitum*. The drinking water was supplemented with 10% solution of defatted colostrum or milk whey for six days. Pilot studies showed that the addition of these solutions did not affect the total volume drunk (mean 5 ml/mouse/day). Small intestinal injury was induced in half of the animals in each group by administering a single dose of indomethacin (85mg/Kg sc.). Animals were killed 24 h later. In order to assess changes in proliferation, each animal also received vincristine (1 mg/Kg i.p.) two hours prior to killing.

Assessment of damage and proliferation:

The wet weight of the various sections of the gastrointestinal tract were recorded and samples of the small intestine and colon (defined by their percentage length) were fixed in Carnoy's fluid and stored in 70% (v/v) ethanol. Tissues were subsequently stained with the Feulgen reaction and the crypts displayed by microdissection. The numbers of arrested metaphases in 20 crypts per animal per site were counted.

Differences in villus height (as an index of intestinal damage) were determined in various regions of the intestine by microdissecting the tissue and tracing the outline of the villi using a stereo dissecting microscope. Tracings were subsequently scanned and analysed by computer image analyses.

2. *In vitro* model of cell proliferation.

Male August rats were anaesthetised and hepatocytes were isolated by *in situ* collagenase perfusion. The digested liver was removed, the cells dispersed, filtered, centrifuged and re-suspended in a plating-medium. For all studies, hepatocytes were grown in Williams E medium without L-glutamine containing 5% foetal calf serum.

Sixteen hours after plating, wells received various concentrations of Epidermal Growth Factor (EGF). EGF was used in these studies to stimulate hepatocyte proliferation. Each well also received 10% colostrum or vehicle (control) to assess the effect of colostrum on EGF stimulated growth. In addition, some wells also received TGFβ or a TGFβ neutralising antibody to examine the effect of TGFβ on cell growth.

The rate of proliferation was assessed by measuring the rate of hepatocyte DNA synthesis. [^{3}H]Thymidine (2μCi/well) was added to each well twelve hours after the addition of EGF (and the other agents) and cells were left for a further 16h before measuring cellular [^{3}H]thymidine incorporation. For each condition, the stimulatory or inhibitory effect of the solutions was measured in quadruplet in four separate wells. Cell viability, determined by the ability to exclude 0.2% trypan blue, was greater than 80% in all experiments.

3. Statistics

Studies were assessed using a two-way ANOVA (with diet and presence of indomethacin as factors for the *in vivo* studies and test solution and presence of TGFβ neutralising antibody as factors for the *in vitro* studies). . Where a significant effect was seen ($P < 0.05$), individual comparisons between groups were performed based on the group means, residual and degrees of freedom obtained from the ANOVA.

RESULTS

In vivo studies

The *in vivo* model of damage to gastrointestinal epithelium allows accurate quantitation of the degree of gastrointestinal injury and is used to determine the protective effects of growth factors involved in mucosal integrity and repair. In these studies, maximal damage occurs 24 hours after administration of indomethacin. Colostrum treated animals have very little damage after this time. This indicates that growth factors in colostrum reduce the degree of initial damage rather than increasing the rate of repair.

Animals which received colostrum or milk solutions but had not been given indomethacin showed no significant changes in gastrointestinal epithelium proliferation or villus morphology compared to control animals.

Indomethacin caused a 25% reduction in the proliferation rate (as determined by 2-hour metaphase assessment, $P < 0.001$) of the small and large intestine in control animals and also those receiving colostrum or milk solution.

At both jejunal and ileal sites, indomethacin also caused a 25% reduction in the villus heights of control animals. Similar changes were seen in animals which had received 10% milk solution. Animals receiving 10% colostrum, however, had only about a 5% reduction in their villus height ($p < 0.001$ compared to control animals receiving indomethacin). This shows that colostrum prevents damage from occurring to gastrointestinal epithelial cells.

In vitro studies

The addition to hepatocytes of increasing doses of EGF caused a dose-dependent increase in ^{3}H thymidine incorporation (an index of the rate of hepatocyte proliferation). Referring to Fig. 1, a control response of 10 mg/ml of EGF increased ^{3}H thymidine incorporation from a basal of approximately 3,000 DPM (1) to about 63,000 DPM (2). The co-administration of 0.1 ng/ml TGFβ with 10mg/ml EGF reduced ^{3}H thymidine incorporation to about 50% (3) suggesting that TGFβ inhibits cell proliferation. This effect was removed when TGFβ neutralising antibody (referred in Fig.1 as Ab for convenience) was also added to the system (4). Significant reductions in ^{3}H thymidine uptake caused by EGF were also seen with 10% colostrum ($P < 0.01$ vs. cells stimulated with EGF alone), the vast majority of this effect was removed when the TGFβ neutralising antibody was also present (5).

The *in vitro* and *in vivo* models demonstrate the value of colostral growth factors in preventing gastrointestinal damage. Addition of colostrum, but not milk, to the drinking water of mice markedly reduced the amount of small intestinal injury caused by indomethacin. The *in vitro* studies show that the predominant biological effect of colostrum preparations is a growth inhibitory response which can be reversed by the addition of a TGFβ neutralising antibody. This indicates that TGFβ plays an essential role in the effect of colostrum on epithelial cells.

EXAMPLE 2

18 Male Sprague Dawley rats (225-250 g) were divided into three groups (six per group). The rats were placed in Bollman restraint cages. One group was given a continuous subcutaneous infusion of saline (control infusion), and the other two groups were given a continuous subcutaneous infusion of TGFβ1 at either 0.15 or 1.5 μg/kg/h. Thirty minutes later all animals received 20 mg/kg of indomethacin (Sigma, UK) subcutaneously. Three hours after the injection of indomethacin, the animals were killed and their stomachs removed. The oesophageal opening was ligated, the stomachs inflated with 4 ml of formalin and the duodenal opening was then ligated to keep the stomachs in an inflated state. Stomachs were left overnight in formalin. The

next day the stomachs were cut open along the greater curve and the total area of ulceration per stomach (mm^2/stomach) was assessed using a dissecting microscope (X10) with the aid of a reference square grid.

Two additional groups (six rats per group) received a single 2 ml gavage of saline or TGFβ (0.5 μg per rat). Both the saline and TGFβ1 solutions also contained 2% hydroxymethylpropylcellulose to slow the rate of gastic emptying, allowing the TGFβ to remain in contact with the stomach for a greater period. Rats were then placed in the restraint cages. 30 min after the gavage, all rats received a single dose of indomethacin 20 mg/kg subcutaneously. Three hours after the administration of indomethacin animals were killed and assessed as above.

The results (mean) for each group are shown in Figure 2. As can be seen from this Figure, TGFβ administered by either route proved to be beneficial in decreasing the amount of injury seen three hours after indomethacine inhibition.

CLAIMS

1. The use of a composition containing at least one compound with Growth Factor-like activity for the manufacture of a medicament for prophylactic treatment of a gastrointestinal condition at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug.

2. The use according to claim 1 wherein the compound(s) with Growth Factor-like activity comprises at least one Growth Factor obtainable from colostrum.

3. The use according to claim 1 or 2 wherein from 0.1 to 5000μgrammes of the said compound(s) is administered daily.

4. The use according to claim 3 wherein from 50 to 2000μgrammes of the said compound(s) is administered daily.

5. The use according to claim 4 wherein from 100 to 1000μgrammes of the said compound(s) is administered daily.

6. The use according to claim 2 wherein the compound is a Transforming Growth Factor β.

7. The use according to claim 6 wherein from 0.05 to 2500μgrammes of said Transforming Growth Factor β is administered daily.

8. The use according to claim 7 wherein from 25 to 1000μgrammes of said Transforming Growth Factor β is administered daily.

9. The use according to claim 8 wherein from 50 to 500μgrammes of said Transforming Growth Factor β is administered daily.

10. The use according to any preceding claim wherein the compound(s) with Growth Factor-like activity is derived from naturally produced Growth Factors that have been isolated from an organism in which they were synthesised. Growth Factors produced by cell culture or fermentation of Growth Factor expressing cells, artificially synthesised Growth Factors, modified Growth Factors produced from genetically engineered organisms, compounds which activate Growth Factor receptors (Growth Factor receptor agonists), compounds which regulate Growth Factor intracellular signalling and compounds which influence growth factor synthesis or breakdown.

11. The use according to any one of claims 1 to 9 wherein the medicament comprises colostrum, or a derivative thereof, containing at least one compound with Growth Factor-like activity.

12. The use according to claim 11 wherein the colostrum or derivative thereof is of bovine origin.

13. The use according to claim 11 or 12 wherein the colostrum is obtained in the first 48 hours post parturition.

14. The use according to claim 11 to 12 wherein the colostrum is obtained from the first and / or second milking post parturition.

15. The use according to any one of claims 11 to 14 wherein a colostrum derivative is used and is in a spraydried form.

16. The use according to any one of claims 11 to 15 wherein a colostrum derivative is used and is a liquid reconstituted from a spraydried colostrum derivative.

17. The use according to claim 15 or 16 wherein from 0.1 to 60.0 grammes of the spraydried colostrum derivative is administered daily.

18. The use according to any one of claims 11 to 14 wherein a colostrum derivative is used and that derivative is colostral whey or a colostral whey derivative.

19. The use according to claim 18 wherein the colostral whey derivative is obtained by ultrafiltration or microfiltration.

20. The use according to claims 18 or 19 wherein from 30 to 300mls of colostral whey or colostral whey derivative is administered daily.

21. The use according to any one of claims 11 - 20 wherein a colostrum derivative is used and that derivative is defatted.

22. The use according to any preceding claim wherein the medicament is administered by an enteral route.

23. The use according to claim 22 wherein the medicament is administered by an enema, a nasogastric tube, gastrostomy tube or jejunostomy tube.

24. The use according to claim 22 or 23 wherein the medicament is administered in the form of a capsule or liquid.

25. The use according to claim 22 wherein the medicament is administered by an oral route.

26. The use according to claim 25 wherein the medicament is administered in the form of a tablet, capsule, liquid, food product or drink product.

27. The use according to claim 26 wherein the food product or drink product contains at least one of carbohydrates, a nitrogen source, vegetable oils, emulsifiers,

oils containing long chain fatty acids, antioxidants, vitamins, soluble fibre, minerals and flavouring.

28. The use according to any preceding claim wherein the composition is administered from 6 to 72 hours in advance of the administration of the non-steroidal anti-inflammatory drug.

29. The use according to claim 28 wherein the composition is administered from 24 to 48 hours in advance of the administration of the non-steroidal anti-inflammatory drug.

30. The use according to any one of claims 1 to 29 wherein the non steroidal inflammatory drug is one of indomethacin, ibuprofen, azapropazone, naproxen, piroxicam, ketoprofen, diclofenac and asprin.

31. A method for the prophylactic treatment of a gastrointestinal condition that is at least partially characterised by damage to epithelial cells and caused by administration of a non-steroidal anti-inflammatory drug, the method comprising administering to a person or animal in need of such treatment a therapeutically effective amount of a composition containing a compound with Growth Factor-like activity.

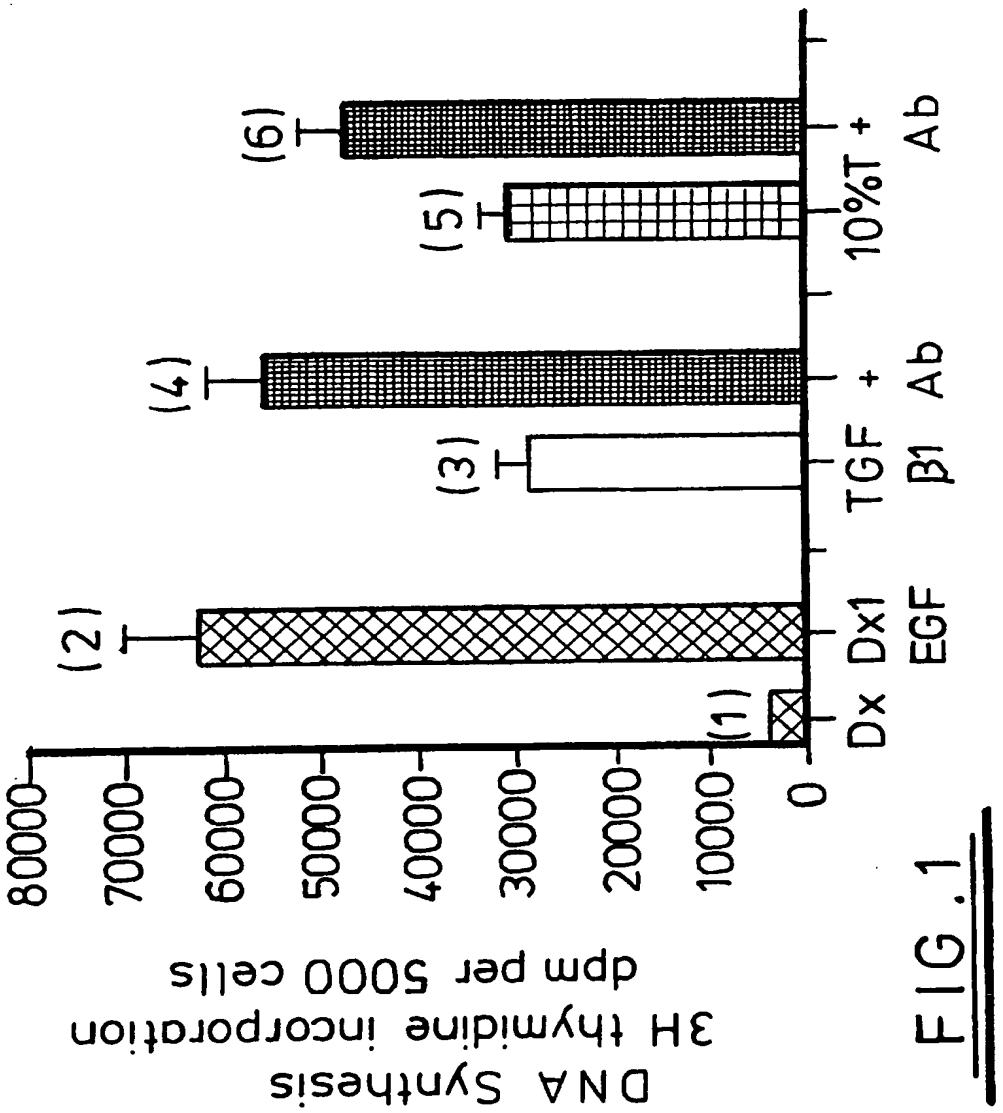
DNA Synthesis
3H thymidine incorporation
dpm per 5000 cells
80000
70000
60000
50000
40000
30000
20000
10000
0
(1)
(2)
(3)
(4)
(5)
(6)
Dx
Dx1
EGF
TGF β1
+ Ab
10%T
+ Ab

FIG. 1

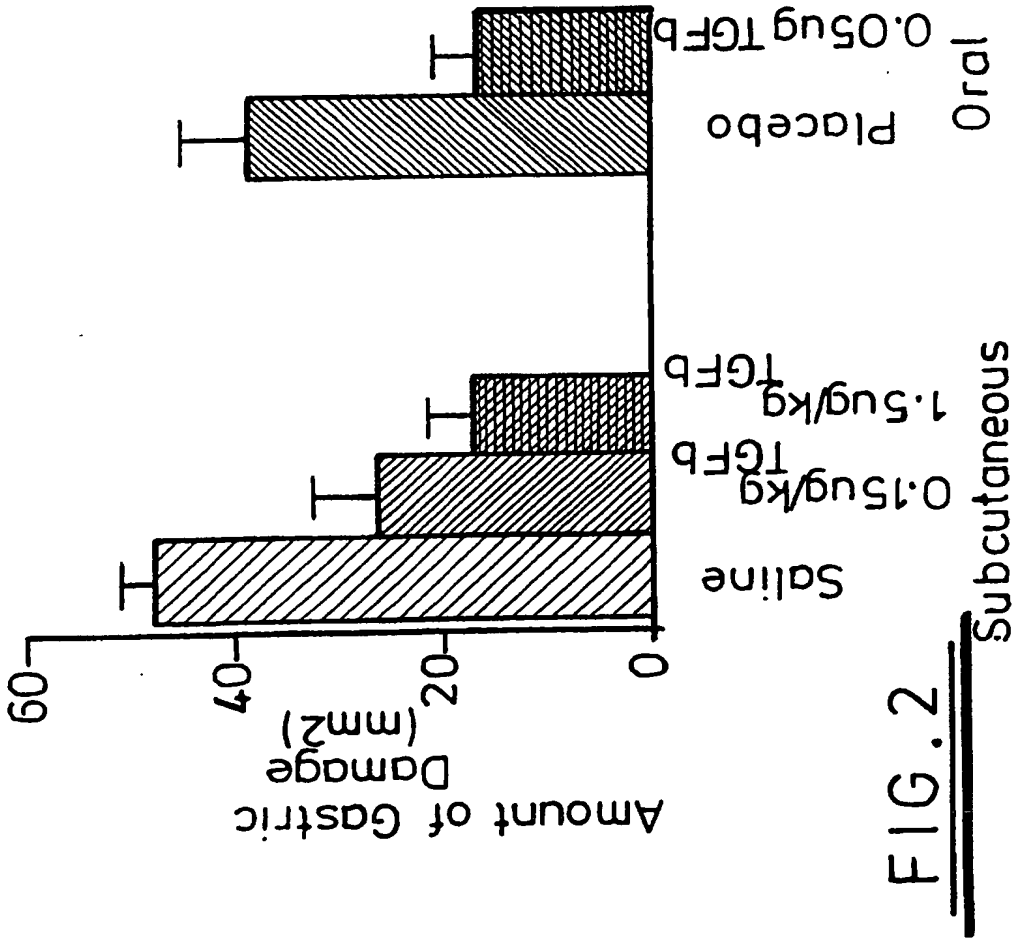
Amount of Gastric Damage (mm2)
0
20
40
60
Saline
0.15ug/kg TGFb
1.5ug/kg TGFb
Placebo
0.05ug TGFb
Oral
Subcutaneous

FIG. 2

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 97/02574

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/18 A61K35/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 34614 A (GROPEP PTY. LTD.) 7 November 1996 see the whole document ---	1-31
X	EP 0 527 283 A (SOCIETE DES PRODUITS NESTLE S.A.) 17 February 1993 see the whole document ---	1-31
X	WO 95 00155 A (VALIO BIOTUOTTEET OY) 5 January 1995 see page 2, line 28 - line 32 see page 3, line 13 - line 28 see page 5, line 19 - line 28; claims ---	1-31
X	EP 0 652 015 A (BRISTOL-MEYERS SQUIBB COMPANY) 10 May 1995 see page 2, line 45 - page 3, line 13; claims --- -/--	1-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 1998	04.03.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

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INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/GB 97/02574

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 00994 A (GROPEP PTY. LTD.) 23 January 1992 see page 4, line 9 - line 25 see page 9, line 17 - page 10, line 5; claims 1-7,18,19,21	1-31
X	WO 95 29933 A (GROPEP PTY. LTD.) 9 November 1995 see page 6, line 4 - line 20 see page 10, line 4 - line 12; claims 1-11,22,24	1-31
X	EP 0 367 447 A (SMITHKLINE BEECHAM CORPORATION) 9 May 1990 see page 4, column 5, line 12 - line 20 see page 7, column 12, line 34 - line 43; claims	1-31
X	EP 0 269 408 A (GENENTECH, INC.) 1 June 1988 see claims 1-6	1-31
X	WO 92 18153 A (CREATIVE BIOMOLECULES, INC.) 29 October 1992 see page 2, line 33 - page 4, line 9; claims	1-31
X	EP 0 619 370 A (AMGEN INC.) 12 October 1994 see page 2, line 39 - page 3, line 28; claims; example 6	1-31
X	WO 93 07891 A (GASTRONE, INC.) 29 April 1993 see page 4, line 6 - line 31 see page 25, line 33 - page 29, line 36; claims	1-31
X	WO 93 14783 A (I. PARIKII ET AL.) 5 August 1993 see page 12, line 21 - page 17, line 23; claims 41-43	1-31

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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 97/02574

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 111, no. 1, 3 July 1989 Columbus, Ohio, US; abstract no. 1522u, S. SUZUKI: "HUMAN EPIDERMAL GROWTH FACTOR IN BREAST MILK, EARLY NEONATAL URINE, AND AMNIOTIC FLUID: SPECULATION ON THE SOURCE AND PHYSIOLOGICAL ROLE." page 152; XP002053998 see abstract & NAGOYA MED. J., vol. 33, no. 2, 1988, pages 91-110, ---	1-31
A	CHEMICAL ABSTRACTS, vol. 103, no. 11, 16 September 1985 Columbus, Ohio, US; abstract no. 82348b, L. JANSSON ET AL.: "MITOGENIC ACTIVITY AND EPIDERMAL GROWTH FACTOR CONTENT IN HUMAN MILK." page 121; XP002053999 see abstract & ACTA PAEDIATR. SCAND., vol. 74, no. 2, 1985, pages 250-253, ---	1-31
P,X	R.J. PLAYFORD ET AL.: "BOVINE COLOSTRUM IS PROPHYLACTIC AGAINST INDOMETHACIN-INDUCED INTESTINAL INJURY." GASTROENTEROLOGY, vol. 112, no. 4 SUPPL., April 1997, BALTIMORE, PA, US, page A394 XP002053545 see right-hand column, last abstract -----	1-31

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INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claim 31 is directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter onal Application No
PCT/GB 97/02574

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